COMMON SEXUALLY TRANSMITTED DISEASES AND THEIR TREATMENT*

WILLIAM M. MCCORMACK, M.D.

Associate Professor of Medicine
Channing Laboratory
Harvard Medical School
Boston, Massachusetts

SINCE its discovery in the early 1950s tetracycline has been greatly relied on to treat many sexually transmitted diseases. Patients with gonorrhea, syphilis, or both who cannot be given a penicillin because of hypersensitivity have been—and still are—treated effectively with tetracycline. Patients with chancroid, lymphogranuloma venereum, granuloma inguinale, and the increasingly common nongonococcal urethritis are given tetracycline as the treatment of choice.

In this paper we shall discuss the use of tetracycline hydrochloride because this is the agent most thoroughly evaluated in the treatment of sexually transmitted diseases. It is likely that the newer tetracyclines, such as doxycycline and minocycline, would be just as effective, and these preparations offer a more convenient dosage regimen.

NONGONOCOCCAL URETHRITIS

Nongonococcal urethritis is not a new problem. Physicians have been aware of this disease ever since gonococci were isolated because shortly thereafter they found a form of "gonococcal" urethritis not caused by gonococci. No one showed much concern over the problem until the early 1960s, when the rapidly increasingly incidence of syphilis and gonorrhea sparked a general alarm. Renewed attention to sexually transmitted diseases led to awareness that the incidence of nongonoccal urethritis was rising at an even more rapid rate than either gonorrhea or syphilis.

Accurate figures for nongonococcal urethritis are not available in the

*Presented as part of *A Symposium on the Tetracyclines: A Major Appraisal* sponsored by the New York Academy of Medicine in cooperation with Science and Medicine Publishing Co., Inc. under a grant from Pfizer Laboratories, New York, N.Y., and held at the Academy October 15, 1977.

Supported in part by U.S. Public Health Service Research Grants HD03693 and A112381 from the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases, Bethesda, Md.

United States because the disease is not reportable. In Great Britain, where all urethritis is reported, it is more prevalent than gonococcal urethritis. Although American statistics are lacking, nongonococcal urethritis appears to be the most common sexually transmitted disease among men in this country. It is by far the most common form of urethritis seen by private physicians and physicians in student health services. Nongonococcal urethritis is more prevalent than gonococcal urethritis among white, affluent suburbanites, and is a disease solely of men. Although sexually transmitted, there appears to be no recognizable counterpart in women. Women seem to be asymptomatic carriers.

Symptoms. Nongonococcal and gonococcal urethritis may be nearly indistinguishable, although the discharge from nongonococcal urethritis may be more mucoid than purulent and less profuse than from gonorrhea. Yet, in some cases the discharge is just as purulent and copious as in gonococcal urethritis. The two diseases do differ in their incubation periods. Symptoms of gonococcal urethritis usually appear two to five days after contact, but for nongonococcal urethritis the period is one to three weeks. Gram stains and cultures of the urethral discharge provide the definitive diagnosis.

Etiology. Virtually every microorganism ever isolated from the male urethra has at one time or another been implicated as the causative agent. *Chlamydia trachomatis* has been established as the cause of more than half of the cases. These organisms (formerly called Bedsonia) are a group of obligate intracellular parasites that differ in biologic characteristics from bacteria, viruses, and mycoplasmas. The etiology of nonchlamydial nongonococcal urethritis is uncertain, although there is increasing evidence that *Ureaplasma urealyticum* (T-mycoplasmas) are responsible for some of the nonchlamydial cases.

Treatment. Tetracycline is the treatment of choice for nongonococcal urethritis. Penicillin is not effective. Tetracycline should be taken for at least seven days at a dosage of 1 to 2 gm./day. When differentiation between gonococcal and nongonococcal urethritis is impossible because of prior antibiotic therapy or lack of laboratory facilities, patients with urethritis can be treated by tetracycline, which will cure both disorders. The patient is given 2 gm./day by mouth for at least one week.

GONORRHEA

Although it is possible for anyone to contract gonorrhea, it is most often

seen in the urban poor. Many suburban physicians see only a few cases a year. If middle-class suburbanites suspect they have gonorrhea, they usually seek medical attention immediately and are compulsive about informing their contacts. Gonorrhea affects both men and women, of course. Chief complaints are frequent voiding, pain, and genital discharge. Gram-stained smears and cultures confirm the diagnosis.

Treatment. Aqueous procaine penicillin G is the antibiotic of choice in a dose of 4.8 million units given intramuscularly in at least two different sites. Before the injections, the patient is given 1 gm. of probenecid orally. If the patient cannot tolerate penicillin, tetracycline is an alternative. A loading dose of 1.5 gm. is given orally, followed by oral doses of 0.5 gm. four times a day for four days. Another alternative to penicillin is spectinomycin hydrochloride, as a single 2-gm. intramuscular injection.

Complications. Pharyngeal gonococcal infections are more difficult to treat than genital infections and may be more common than previously thought. Unless the patient gives a history of penicillin allergy, penicillin is the treatment of choice. If the patient cannot take penicillin, tetracycline is the only alternative, as the efficacy of spectinomycin in the treatment of gonococcal pharyngitis has not been established. Moreover, tetracycline can be given to treat pharyngeal infections that do not respond to penicillin. A loading dose of 1.5 gm. is given at the outset, followed by 2 gm./day of tetracycline for four days.

One of the most difficult treatment problems is a pregnant patient with gonorrhea who is allergic to penicillin because there are no comfortable alternatives to penicillin. Tetracycline is contraindicated because it will be incorporated into the forming fetal teeth and cause staining. Erythromycin may be given, but it is ineffective about 25% of the time. Spectinomycin is effective, but its safety for use during pregnancy has not been established.

Follow-up. All patients treated for any form of gonorrhea should be evaluated with a posttreatment culture. Cultures should be obtained seven to 14 days after completion of therapy, and treatment failures should be treated with spectinomycin. Pharyngeal treatment failures should be given tetracycline.

Gonococcal resistance. Since 1943, when penicillin was first found effective in treating gonorrhea, the recommended dosage has gradually increased. In the mid-1940s, 160,000 units of penicillin sodium was effective. Today, 30 years later, 4.8 million units of procaine penicillin G plus 1 gm. of probenecid is recommended.

The increase in resistance happened step by step, as mutations among the gonococci created organisms that had a selective advantage, and these thrived and resisted the then current doses of penicillin. Of course, the resistance could be overcome by increasing the amount of penicillin. The contest between mutation and drug continued until the Center for Disease Control intervened.

In 1972 the Center for Disease Control reasoned that a superdose of penicillin would annihilate almost all contemporary strains of gonococci, leaving few survivors with a selective advantage, and recommended the current dosage regimen. The penicillin onslaught seemed to work, and gonococcal resistance to penicillin and tetracycline began to level off. Gonococci isolated in late 1975 were actually more sensitive to penicillin and tetracycline than those isolated in 1971. However, any feelings of complacency were short-lived. Early in 1976 a few cases of gonorrhea appeared in the United States that did not respond to this regimen or even higher doses of penicillin. It was soon apparent that these gonococci carried an extrachromosomal DNA segment called a plasmid, or R-factor (R for resistance). These gonococci produce an enzyme called penicillinase, or beta-lactamase, which splits the penicillin molecule and renders the drug ineffective.

Penicillinase-producing gonococci were first reported in early 1976. When they appeared in the United States it was feared that soon penicillin would be ineffective in treating gonorrhea. So far, however, these penicillinase-producing gonococci have not lived up to expectations. They have been in this country for almost two years now and are still a curiosity. To date, only about 200 cases have been reported, while about 1,000,000 cases of gonorrhea are reported to the Public Health Service each year. Nevertheless, the appearance of these resistant gonococci suggests that gonorrhea therapy may soon need reevaluation. If penicillinase-producing gonococci were to increase and cause 5 to 10% of new cases of gonorrhea, it would be necessary to devise a new therapeutic program.

Spectinomycin could become the new drug of choice if penicillin became ineffective. Currently it is the most effective possible alternative. (Tetracycline would not be a wise alternative because strains of bacteria resistant to penicillin are usually resistant to tetracycline.) Spectinomycin, however, is not the complete answer because it may not be effective against pharyngeal gonococcal infections. Further, resistance to spectinomycin is easily induced in the laboratory, and increased use of this

agent would probably eventually lead to a plasmid-mediated spectinomycin resistance. Spectinomycin could lose its effectiveness in a short period of time.

To slow the spread of penicillinase-producing gonococci, the Center for Disease Control recommends that patients treated for gonorrhea be carefully cultured following therapy. Isolates from patients who fail to respond to penicillin should be examined for the production of penicillinase. All state health department laboratories have received instructions on how to perform these tests. Aggressive contact tracking should be carried out to identify and treat the sexual partners of persons known to be infected with penicillinase-producing gonococci.

SYPHILIS

Epidemiology. Syphilis is 20 times less prevalent than gonorrhea, but nonetheless remains a serious problem. Like gonorrhea, it is primarily a problem of poor inner-city residents. Poor or not, homosexual men are often afflicted, and some studies show that about two thirds of patients treated for syphilis are homosexual men.

The treatment of choice for primary, secondary, and latent syphilis of less than one year's duration is a single injection of 2.4 million units of benzathine penicillin G given intramuscularly at a single session. Patients who cannot be given penicillin can be treated with tetracycline, 2 gm. daily, by mouth, for 15 days. Patients with latent syphilis of more than one year's duration or patients with tertiary syphilis are treated with benzathine penicillin G, 2.4 million units, intramuscularly, each week for three successive weeks. Patients with latent syphilis of more than one year's duration or with tertiary syphilis who are allergic to penicillin can be given tetracycline as an alternative. The dosage is 2 gm./day for 30 days. Again, pregnant patients present a difficult problem if they are allergic to penicillin. Pregnant women should not be given tetracycline because of staining of the fetal teeth. They can be given erythromycin in the dosage schedule outlined above for tetracycline.

Follow-up. Follow-up is important in all patients treated for syphilis. They should be seen at three-month intervals for at least one year.

Sexual partners of patients with primary, secondary, or early latent syphilis should be evaluated. Therapy is recommended following the schedule outlined above.

Chancroid, Lyphogranuloma Venereum, and Granuloma Inguinale

These three sexually transmitted diseases are characterized by genital ulcers. Tetracycline therapy is the recommended treatment. Patients should receive 1 to 2 gm./day for two to four weeks.

Classic Candidates

Nongonococcal urethritis. A 19-year-old male college student comes to the student health service complaining of frequency and pain on urination. He says he has noted a cloudy urethral discharge. Although he has a regular girl friend, he says that about a month ago he spent a weekend with an old girl friend. A Gram-stained smear of his urethral discharge contains polymorphonuclear leukocytes and no intracellular diplococci. A culture of the discharge is negative for gonococci.

Gonorrhea. A young female college senior says that her boy friend has been treated for gonococcal urethritis. On questioning, she reports having no other sexual partners. She engages in intravaginal intercourse and fellatio with her boy friend. She states that she is allergic to penicillin.

Syphilis. A young man complains of a generalized skin rash that does not itch and that involves the palms of his hands and the soles of his feet. The patient says that he is homosexual and that he is involved in a monandrous relation with his roommate. About eight weeks ago he visited a gay bath and had sexual contact with three unknown individuals. He also reported that he received a shot of penicillin for gonorrhea about two years ago and had a severe reaction: hives and difficulty in breathing.

Treatment. Each of the patients can be effectively treated with tetracycline.

REFERENCES

1. McCormack, W. M.: Sexually transmissible diseases. *Postgrad. Med. 58*: 179, 1975.
2. McCormack, W. M.: Management of sexually transmissible infections during pregnancy. *Clin. Obstet. Gynecol. 18*:57, 1975.
3. King, A.: Nonspecific urethritis. *Med. Clin. North Am. 56*:1193, 1972.
4. Jacobs, N. F. and Kraus, S. J.: Gonococcal and nongonococcal urethritis in men. Clinical and laboratory differentiation. *Ann. Intern. Med. 82*:7, 1975.
5. Holmes, K. K., Handsfield, H. H., Wang, S. P., Wentworth, B. B., Turck, M., Anderson, J. B., and Alexander, E. R.: Etiology of nongonococcal urethritis. *N. Engl. J. Med. 292*:1199, 1975.
6. Bowie, W. R., Wang, S. P., Alexander, E. R., Floyd, J., Forsyth, P. S., Pol-

lock, H. M., Lin, J.-S. L., Buchanan, T. M., and Holmes, K. K.: Etiology of nongonococcal urethritis. Evidence for *Chlamydia trachomatis* and *Ureaplasma urealyticum*. *J. Clin. Invest.* *59*:735, 1977.
7. John, J.: Efficacy of prolonged regimes of oxytetracycline in the treatment of nongonococcal urethritis. *Br. J. Vener. Dis.* *47*:266, 1971.
8. Center for Disease Control: Gonorrhea—CDC recommended treatment schedules, 1974. *Morbid. Mortal. Weekly Rep.* *23*:341, 1974.
9. McCormack, W. M.: Treatment of gonorrhea—Is penicillin passé? *N. Engl. J. Med.* *296*:934, 1977.
10. Center for Disease Control: Syphilis—CDC recommended treatment schedules, 1976. *Morbid. Mortal. Weekly Rep.* *25*:101, 1976.